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STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
STOCKTON, LAURA	
ART UNIT	**PAPER NUMBER**
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/975,881	GRIBKOFF ET AL.	
	Examiner	Art Unit	
	Laura L. Stockton, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/05/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-45 are pending in the application.

Election/Restrictions

Applicants' election without traverse of Group I, reproduced below, and the species of Example 2 (the structure of BMS-204352 on pages 13 and 27), in the response filed October 1, 2003 was acknowledged in the previous Office Action.

I. Claims 1-45, drawn to a method of use wherein the maxi-K potassium channel opener is a fluoro-oxindole compound or a chloro-oxindole compound, classified in class 514, subclass 418.

Subject matter not embraced by elected Group I is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions. Election was made **without** traverse in the response filed October 1, 2003.

Information Disclosure Statement

The Information Disclosure Statement filed on February 5, 2004 has been considered by the Examiner.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10, 12-17, 19-26, 28-40 and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Hewawasam et al. {U.S. Pat. 5,565,483} or Hewawasam et al. {U.S. Pat. 5,602,169}.

Hewawasam et al. '483 disclose Example 14 (column 25) that is an opener of the large-conductance calcium-activated potassium channels (also known as maxi-K channels) and is useful in treating diseases or disorders (e.g., ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels (column 1, lines 5-13, 31-33 and 47-53; column 13, lines 21-67; column 14, lines 1-34; column 15, lines 43-64; and Example 14 in column 25, lines 40-52).

Hewawasam et al. '169 disclose Example 14 (column 26), Example 37 (column 31) and Example 38 (column 31) which are openers of the large-conductance calcium-activated potassium channels and are useful in treating diseases or disorders (e.g., ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels (column 1, lines 12-19; column 3, lines 1-63; column 13, lines 19-57; Example 14 in column 26, lines 36-51; and Examples 37 and 38 in column 31, lines 26-56).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hewawasam et al. {U.S. Pat. 5,565,483} and Hewawasam et al. {U.S. Pat. 5,602,169}, each taken alone or in combination with each other.

Determination of the scope and content of the prior art (MPEP §2141.01)

Applicants claim a method of treating a disease or disorder characterized by high intracellular calcium levels comprising providing an effective amount of an opener of maxi-K potassium channels (e.g., fluoro-oxindole and chloro-oxindole compounds). Each of Hewawasam et al. '483 (column 1, lines 5-13, 31-33 and 47-53; column 13, lines 21-67;

column 14, lines 1-34; column 15, lines 43-64; and Example 14 in column 25, lines 40-52) and Hewawasam et al. '169 (column 1, lines 12-19; column 3, lines 1-63; column 13, lines 19-57; Example 14 in column 26, lines 36-51; and Examples 37 and 38 in column 31, lines 26-56) teach fluoro-oxindole compounds, which are openers of the large-conductance calcium-activated potassium channels (also known as maxi-K channels), and are useful in treating diseases or disorders (e.g., ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between some of the openers of maxi-K potassium channels used in the methods of use taught by the Hewawasam et al. references and the openers of maxi-K potassium channels used in the instant claimed method of use is that the openers of maxi-K potassium channels used in the instantly claimed method of use are generically

described in the prior art (e.g., see the openers of maxi-K potassium channels in instant claim 8).

The difference between some of the openers of maxi-K potassium channels used in the methods of use taught by the Hewawasam et al. references and the openers of maxi-K potassium channels used in the instantly claimed method of use (e.g., see the openers of maxi-K potassium channels in instant claim 11) is that of a fluoro-oxindole opener instead of a chloro-oxindole opener.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

The indiscriminate selection of "some" among "many" is *prima facie* obvious. The motivation to make additional compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g., an opener of maxi-K channels).

Further, in *Ex parte Wiseman*, 98 USPQ 277 (1953), it was held that compounds are rejected over prior art when the difference between

the claimed compounds and the compounds of the prior art is two fluorine atoms versus chlorine atoms. The basis of this reasoning is that fluorine and chlorine are both halogen elements from the seventh group of the periodic system and the claimed compound is thus an analogue or an isologue of that disclosed in the prior art. The compounds are expected to possess similar properties differing only in degree.

One skilled in the art would thus be motivated to prepare openers embraced by the teachings in the Hewawasam et al. references, or alternatively, prepare the chloro-oxindole openers instead of the fluoro-oxindole openers, to arrive at the instant claimed invention with the expectation of obtaining additional beneficial openers of maxi-K potassium channels and that the obtained fluoro- or chloro-oxindole openers would be useful in treating diseases or disorders such as stroke, traumatic brain injury, etc. The instant claimed invention (a method of treating a disease or disorder by providing an opener of maxi-K potassium channels such as a fluoro-oxindole or a chloro-oxindole compound) would have been suggested to one skilled in the art and

therefore, the instant claimed invention would have been obvious to one skilled in the art.

Response to Arguments

Applicants' arguments filed April 22, 2004 have been fully considered. Since the arguments presented by Applicants to the Office are relatively the same for the rejection of the claims under 35 USC §§ 102(b) and 103, the responses to these arguments have been combined to cover both prior art rejections.

Applicants argue that neither of the Hewawasam et al. references teach methods of treatment or compounds which selectively open maxi-K channels disposed in neuronal cells having high intracellular calcium levels while not opening maxi-K channels disposed in neuronal cells having a normal physiological calcium concentration. Applicants argue that the Office has misconstrued Applicants' invention in that Applicants are claiming a method and not an opener. Applicants argue that they are

claiming various methods in which neuronal cells are selectively targeted for maxi-K channel opening based on intracellular calcium concentration. Applicants further argue that the methods claimed in the subject application are directed to the discovery that neuronal cells that express maxi-K channels, but do not have elevated intracellular calcium levels, are not targeted by the compounds used as exemplary compounds in the Laboratory Examples found in the instant specification. Applicants state that the openers themselves are not being claimed but rather methods of treating conditions wherein a maxi-K opener is employed to open only those channels that are present in neuronal cells in which high intracellular calcium conditions are present.

All of Applicants' arguments have been carefully considered but have not been found persuasive. Instant claim 1 has been reproduced below.

> 1. (Original) A method of treating a disease or disorder characterized by high intracellular calcium levels in an individual in need thereof, comprising:
>
> providing an effective amount of an opener of maxi-K potassium channels to said individual, wherein said opener activates maxi-K potassium channels in cells under conditions of high intracellular calcium concentration, and does not significantly activate maxi-K potassium channels in cells under low or normal concentrations of intracellular calcium.

Claim 1 is directed to treating a disease or disorder by providing an effective amount of an opener of maxi-K potassium channels. Per the instant specification on page 6 (lines 31-32) and page 7 (lines 1-5), reproduced below, a treatable disease or disorder embraced by instant claim 1 is, for example, a stroke. Also see instant claims 3 and 4, reproduced below.

> It is yet a further particular object of the present invention to provide methods for the treatment or prevention of neurological diseases,
>
> particularly stroke, and more particularly, acute ischemic stroke, in mammals, preferably humans, employing openers of maxi-K channels having the selective ability to target and activate maxi-K channels in cells having high levels of intracellular Ca^{2+} (e.g., ischemic neurons), while not significantly targeting and activating non-ischemic or normal neurons.

3. (Original) The method according to claim 1, wherein the disease or disorder is a neurodegenerative disease or disorder.

4. (Original) The method according to claim 3, wherein the neurodegenerative disease or disorder is selected from the group consisting of stroke, global cerebral ischemia, traumatic brain injury, Parkinson's disease, epilepsy, migraine and Alzheimer's disease.

Per the instant specification on page 13 (lines 3-20), reproduced below, Applicants disclose that fluoro-oxindole compounds are found in each of the above cited prior art and that the fluoro-oxindole compounds are capable of acting selectively as maxi-K channel openers on cells having high intracellular calcium concentration. Also on page 13 of the instant specification, Applicants disclose a specific opener of maxi-K potassium channels which is (3S)-(+)-(5-chloro-2-methoxy phenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one (also known as BMS-204352). BMS-204352 is Applicants' elected species (e.g., an opener) for use in the instant claimed method of use. As stated in the previous Office Action, a method of treating a disease or disorder (such as a stroke) by providing an effective amount of an opener, which is the elected species BMS-204352 of the present application, is not allowable since, for instance, Example 37 (column 31) is disclosed in Hewawasam et al. '169 and is BMS-204352.

> One class of compounds having selective function on cells having high intracellular calcium concentrations encompasses the 3-phenyl substituted oxindole derivatives, as described in U.S. Patent Nos. 5,565,483 and 5,602,169 to P. Hewawasam et al., the contents of which are incorporated by reference herein. Fluoro-oxindole compounds are within the above-described class and are capable of acting selectively as maxi-K channel openers on cells having high intracellular calcium concentration, and not acting to an appreciable extent to open maxi-K potassium channels in cells having normal, moderate or low intracellular calcium concentration.
>
> One member of the fluoro-oxindoles is the maxi-K opener compound (3S)-(+)-(5-Chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one, or BMS-204352, which has been newly determined according to this invention to be a selective and effective opener of a human brain maxi-K channel α-subunit, *hSlo*, (S. Dworetzky et al., 1994, *Brain Res. Mol. Brain Res.*, 27:189-193) expressed in human embryonic kidney (HEK-293) cells under conditions of elevated or high intracellular calcium concentration.

It appears that Applicants are arguing the action or mechanism in which the disease or the disorder is treated. However, as stated in the previous Office Action, a compound and its properties are inseparable. *In*

re Papesch, 137 USPQ 43 (CCPA 1963). As detailed above, the same known in the art maxi-K channel openers are used to treat the same diseases or disorders which are known in the art to be treatable by known in the art maxi-K channel openers. Therefore, the rejection of the claims under 35 USC §§ 102(b) and 103 are deemed proper and are maintained.

A method of treating a disease or disorder (such as cerebral ischemia) by providing an effective amount of an opener, which is the elected species (e.g., BMS-204352 found on pages 13 and 27), is not allowable. See, for instance, Example 37 in column 31 of U.S. Pat. 5,602,169 and the methods of use disclosed therein such as in column 13, lines 41-53.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application contains subject matter drawn to inventions nonelected without traverse in the reply filed on October 1, 2003. A complete reply, if any, to the final rejection must include cancellation of the nonelected subject matter (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Laura L. Stockton, Ph.D.
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

June 30, 2004